REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-15, 38, 39, 41, 48-52 and 67-79 will be pending in the application subsequent to entry of this Amendment.

Amendments to the Claims

New claims 72 to 79 have been added. Basis for the claims is original claim 1 together with the description of the PCT application as published as follows:

72-73	Page 48, line 7 and Table 11.
74-77	Page 17, lines 16-18 (and page 27, lines 24-26).
78	Page 48, line 7 and Table 11 and page 17, lines 16-18 (and page 27, lines 24-26).
79	Page 48, Table 11.

Examiner's Objections

Previously pending claims

(a) The examiner has rejected the previously pending claims on file as being obvious over Eriksen et al. (*J. Pharm. Pharmacol.* **1989**, *41*, 803-805), in view of Watts et al. (WO 98/47535). It is the opinion of the examiner that the skilled person would have incorporated pectins having a low degree of esterification, as disclosed in Watts, into the solutions of Eriksen, in order to produce a solution suitable for intranasal administration for the treatment of analgesia.

The examiner argues that the skilled person would have been motivated to introduce the gelling capacity taught by Watts into the solutions of Eriksen because:

> "*...this would improve the duration of the desired plasma concentration of the active agent delivered from the compositions in the method taught by Eriksen et al. through enhanced retention in the nasal cavity.*"

The examiner believes that the skilled person would have expected success because:

> "*...the mucoadhesives are designed for effecting retention of active agents in nasal spray solutions in the nasal cavity upon administration.*"

The applicant respectfully disagrees with the examiner's arguments. Buprenorphine is a weakly basic compound having a pKa of about 8.3, which is almost identical to that of nicotine, which has a pKa of about 8.5. Formulations comprising nicotine together with pectins having a

low degree of esterification are exemplified in Watts (page 25, Example 2), which refers to the compound as a weak base. In tests to determine the ability of such formulations to gel as expected when contacted with nasal electrolyte solutions it was found by Watts that no gelation occurred when nicotine was used. In contrast, formulations comprising a weak acid (sodium cromoglycate) gellation was found to occur.

Watts attempts to explain the failure of nicotine formulations to gel by offering an un-supported theory related to interactions of ionized nicotine with charged carboxyl groups on the pectins (page 25, lines 21-24). This theory is not backed up by either evidence or any reasonable scientific rationale.

Furthermore, Watts then proceeds (page 25, lines 24-26) to suggest that the skilled person is able to overcome this complete failure by adjusting the pectin concentration to take this into account. There is no hint at how the skilled person may adjust the concentration of pectins (higher/lower?) to achieve this goal. Nor is there any mention of any source of common general knowledge or other art that the skilled person would refer to in order to find a solution to the problem. Finally, Watts does not provide any solution to the problem or demonstrate that the problem can indeed be solved. Even though the solution to the problem is apparently so obviously straightforward, Watts has failed to complete the work by providing experimental details for a nicotine formulation that does in fact gel when exposed to a nasal electrolyte solution.

The skilled person reading Watts would be left with the simple conclusion that formulations of weak bases do not gel when the teaching of Watts is followed. The skilled person would therefore have no motivation to use the pectins of Watts in the solutions of Eriksen, because there would be an expectation that such formulations would not gel and would not have any other beneficial properties.

The present claims are therefore not rendered obvious based on Eriksen in view of Watts.

(b) The aim of the present invention is to identify a composition of buprenorphine that can be administered more readily by a patient than intravenous administration while providing a comparable rapid onset of pain relief (*see* published PCT application at page 3, 1st para.).

The examiner's assertion that incorporating the pectins of Watts into the formulations of Eriksen "*would improve the duration of the desired plasma concentration*" is clearly without foundation.[1] The skilled person would not consider combining the teachings of Eriksen and Watts with the intention of enhancing retention of the agent in the nasal cavity if this effect was achieved with detriment to the fast onset of pain relief. Adapting a composition suitable for intranasal administration to result in prolonged administration of buprenorphine but which reduced the fast onset of analgesia would not provide any advantage over other results of administration, such as sublingual administration.

The examiner has also stated that rapid uptake of the drug is an "*inherent*" property of the Eriksen formulations. The formulations are aqueous solutions and the skilled person would expect from the teaching of Watts that incorporation of a gelling agent would result in retardation of absorption.

Apomorphine is among the list of drugs considered by Watts to be suitable for application of the disclosed technology (page 14, line 22). As noted above, the evidence is such that apomorphine formulations, just as with nicotine formulations, would not gel. However, in any event, apomorphine gelling formulations would be expected by Watts to retard absorption of the drug thereby avoiding the side effects usually observed with high peak plasma levels (page 14, lines 17-18). However, as disclosed in the present application at page 1, this is a problem not experienced by buprenorphine, unlike other opioids. There is therefore no motivation in Watts that would lead the skilled person to use the disclosed compositions for intranasal administration of buprenorphine with rapid onset (short T_{max}) and high bioavailability.

The present claims are therefore not rendered obvious based on Eriksen in view of Watts.

(c) In addition, new claims 72-79 include specific limitations to a short T_{max} and/or high bioavailability which are not features that the skilled person would expect to be achievable based on the prior art as discussed above.

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[1]Counsel notes the examiner's findings must be based on substantial evidence, i.e., some concrete evidence in the record. *See In re Zurko*, 258 F.3d 1379, 59 USPQ2d 1693 (Fed. Cir. 2001). ("[T]he Board cannot simply reach conclusions based on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings.") Applicant provides herewith evidence that disproves the basis for the rejection and the examiner is obliged to accept this evidence as correct or provide substantial evidence (not argument) to the contrary.

The examiner has argued that, even though there are differences between the pharmacokinetic parameters of the invention (C_{max} and T_{max}) and those of Eriksen, such parameters can be optimized by routine experimentation.

The applicant strongly disagrees with the examiner's statement that optimization of pharmacokinetic parameters, such as T_{max}, can be achieved by routine experimentation. Neither T_{max} nor bioavailability would be expected to be significantly altered by routine adjustments of concentrations of drug, solvents or carriers. The examiner is also of the opinion that there is no "criticality" of these characteristics. This is not so -- T_{max} and bioavailability are two of the most critical parameters associated with any drug and particularly in the present case which is directed at the analgesic, buprenorphine.

Intravenous administration provides an instant T_{max} and other modes of administration are unlikely to match this. However, it is clearly a desirable goal in the field of pain relief to provide a composition (for non-i.v. administration) that can provide systemic delivery of an analgesic, such as buprenorphine, as rapidly as possible (i.e. with a short T_{max}). It is also a desirable objective to maximize the bioavailability of the drug delivered in order to reduce the dosage administered to a patient.

The skilled person seeking to develop compositions of buprenorphine having a short T_{max} and/or improved bioavailability would be aware from Eriksen that an inhaled formulation can provide a T_{max} of 30.6 minutes and a bioavailability of 48%. Eriksen does not provide any guidance, insight or motivation to the skilled person seeking to provide a reduction in this T_{max} and/or an enhancement in the bioavailability.

There is also no disclosure, express or implied, in Watts that addresses these issues. Watts refers solely to the preparation of compositions that gel on, *inter alia*, intranasal delivery. In fact, Watts clearly states that the compositions disclosed do not, and would not be expected to enhance the bioavailability of the drug (*see* pages 27-29, Example 3).

In particular, Example 3 is entitled

> "*To Demonstrate that Nasal Formulations containing Low DE Pectin do not Enhance the Systemic Uptake of a Poorly Soluble Drug*"

and concludes (page 29, lines 7-8) with the statement:

> "*...the presence of pectin in the formulation did not lead to an increase in the systemic bioavailability of the model drug*".

The skilled person seeking to improve the bioavailability of the buprenorphine compositions disclosed by Eriksen would not consider the teaching of Watts as suitable for such a purpose. In fact, Watts teaches away[2] from the present invention, which discloses compositions having a significantly improved bioavailability over those of Eriksen.

Additionally, the compositions disclosed by Watts are designed to retard the absorption of a drug as stated at page 13, lines 14 -16:

> "*If the therapeutic agent is easily absorbed, absorption may be retarded, thus keeping more of the drug at the site of application where it is needed*".

For readily absorbable drugs which are intended to act systemically, Watts also teaches that the disclosed compositions will "*retard absorption*". In both cases therefore Watts teaches compositions suitable for increasing T_{max} and not reducing it in accordance with the present invention. The aim of the present invention is to utilize the nasal cavity as a route of administration to provide rapid systemic delivery of an analgesic, in order to provide rapid relief from pain, and delayed onset as would be expected from the teaching of Watts is neither beneficial nor desirable.

The present claims are therefore not rendered obvious based on Eriksen in view of Watts.

There is no further teaching in either Reich or Nairn which would lead to the subject matter of the present claims. The claims are therefore not obvious in view of these documents.

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[2] An important consideration in determining obviousness is "teaching away" from the claimed invention by the prior art. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). A reference teaches away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. A reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also KSR Int'l. Co v Teleflex Inc.*, 127 S. Ct. at 1739–40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious).

Double Patenting

An objection on the ground of non-statutory obvious-type double patenting has been made based on US Patent No. 6,387,917 in view of Eriksen, Watts and Ni. The subject-matter of the present claims is not obvious over the '917 patent for the same reasons discussed above.

An objection on the ground of non-statutory obvious-type double patenting has also been raised based on co-pending application 11/798,384. As this objection is only provisional applicants will address it at a later date when allowable subject matter is indicated.

For the above reasons, it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and allowance are solicited.

Respectfully submitted,

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